UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,915	03/23/2004	Frances Louisa Titus	48170.00040/PC832.00	4427

67676 7590 04/02/2010

Medtronic
Attn: Noreen Johnson - IP Legal Department
2600 Sofamor Danek Drive
Memphis, TN 38132

EXAMINER	
JOIKE, MICHELE K	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
04/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,915	TITUS ET AL.	
	Examiner	Art Unit	
	Michele K. Joike	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 44-49* is/are pending in the application.

4a) Of the above claim(s) *1-6,16-20,31-35 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-15, 21-20, 36-40, 44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed January 8, 2010. Claims 1-41 and 44-49 are pending in the application. Claims 7-15, 21-30, 36-40 and 44-49 are currently under examination.

Any rejection of record in the previous Office Action, mailed July 14, 2009 that is not addressed in this action has been withdrawn. Because this Office Action introduces new rejections other than those set forth in the previous Office Action, and are not necessitated by amendment, this Office Action is Non-Final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9, 12-15, 21-23, 26-30, 36-38, 44, 46 and 48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Boden et al. (Endocrinology 1998, vol. 139, no.12, pages 5125-5134), in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998. Vol.6, pages 306-317), and in further view of Liu et al.

This rejection is maintained for reasons of record, and as discussed below.

Claims 7-15, 24, 25, 36-40, 44, 45 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hair et al (US 6,521,750) or (US 6,858,431) in view of Nagahara et al.

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Hair et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or mesenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (see col.4 5th paragraph). Hair et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces

bone nodule formation and mineralization (see col. 19 bottom paragraph through col.20 top paragraph). LMP-1s disclosed by Hair et al. is a truncated version of LMP-1 that has been demonstrated with osteoinductive activity. As such, it meets the limitation of an isolated osteoinductive region of an LMP-1 protein. Furthermore, it teaches SEQ ID NO: 7. Amino acids 120-149 of SEQ ID NO: 10 are identical to SEQ ID NO: 7 of the instant application. Hair et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see col.20 bottom paragraph through col.21 4th paragraph). Hair et al. also demonstrate that a fusion of HIS tagged human LMP-1 also induces bone nodule formation (see col. 22, 1st paragraph).

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

Furthermore, a fusion polypeptide comprising a protein transduction domain and an osteoinductive polypeptide comprising an osteoinductive region of an LMP-1 protein is taught. SEQ ID NO: 10 of Hair et al is an osteoinductive polypeptide containing an osteoinductive region (SEQ ID NO: 7). As just discussed, Nagahara teaches the fusion protein comprising a protein transduction domain.

It would have been obvious to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Hair et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Hair already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. One would be motivated to use osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, because Hair et al teach that the short version (LMP-1s) is fully functional when expressed in cell culture and in vivo. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Claims 10, 11, 24, 25, 39, 40, 45, 47 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boden et al. (Endocrinology 1998, vol. 139, no.12, pages 5125-5134), in view of Nagahara et al. and van Beuningen et al. (Osteoarthritis and Cartilage, 1998. Vol.6, pages 306-317), and Liu et al as applied to claims 7-9, 12-15, 21-23, 26-30, 36-38, 44, 46 and 48 above, and further in view of WO99/06563.

Boden et al. teach ex vivo transfection of bone marrow cells, osteogenic precursor cells or msenchymal stem cells with nucleic acid that encodes LMP or HLMP, followed by reimplantation of the transfected cells in the donor for treating bone-related disorder and inducing new bone formation (page 5133, Figure 9). Boden et al. also teach introducing expression vector encoding human LMP1 into rat calvarial cells induces bone nodule formation and mineralization. Boden et al. further teach that expression of LMP in bone progenitor cells induces differentiation (see page 5131, Figure 6). Boden et al. also demonstrate that LMP induces genes such as BMP-2 expression and thus is an important regulator for osteoblast differentiation (see page 5132, 2nd col., 1st paragraph).

However, Boden et al. do not teach a method of inducing bone formation in a mammal or inducing osteoblast differentiation in a progenitor cell comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one osteoinductive polypeptide. Boden et al. do not each LMP induces proteoglycan production in a mammal, or an osteoinductive polypeptide that has less than 100% homology to LMP-1, RLMP and LMP-1s.

Nagahara et al. teach a method of transducing full length TAT fusion proteins into mammalian cells. Nagahara et al. demonstrate that TAT-p27 induces cell migration in hepatocytes transduced with this fusion protein (see page 1451, 1st col., 2nd paragraph). Nagahara et al. further teach that TAT fusion proteins may be transduced into a variety of cell types including bone marrow stem cells, osteoclasts, osteosarcoma etc (see page 1450, 1st col.) Nagahara et al. also teach different fusion proteins of TAT which are capable of induce biological response in vivo (see page 1451, Table 1).

van Beuningen et al. teach that the synthesis of proteoglycan including aggrecan is increased following BMP-2 injection to the knee of a rat model (see page 309, 2nd col., 1st paragraph).

Liu et al (J. of Bone and Mineral Res. 17(3): 406-414, 2002, especially p. 406) teach a truncated version of hLMP-1, LMP-1(t). LMP-1(t) would have a different amino acid sequence from LMP-1, since it is full length, and RLMP, since the peptide is rat and not human, and absent evidence to the contrary is different from LMP-1s, because as noted above, there is no indication what the peptide sequence is for LMP-1s, and the specification of the instant application teaches that it can be SEQ ID NO:s 1-8, which are much shorter that the 223 amino acids of LMP-1(t).

However, none of the references teach SEQ ID NO: 7.

WO99/06563 (see entire reference, especially p. 59 and amino acids 120-149 of SEQ ID NO: 10) teaches a method for inducing bone formation using an intracellular signalling molecule that participates early in the cascade of events that leads to bone

formation, using LMP. Amino acids 120-149 of SEQ ID NO: 10 are identical to SEQ ID NO: 7 of the instant application.

It would have been obvious to one of ordinary skill in the art to one of ordinary skill in the art to make TAT-LIM fusion proteins to induce bone formation and progenitor cell differentiation, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, based on the combined teaching of Boden et al., Nagahara et al and Liu et al. One of ordinary skill in the art would be motivated to do so because cellular manipulation by transfection or viral introduction of cDNA expression vectors presents various difficulties including massive overexpression, broad cell to cell intracellular concentration rages of expressed protein and low percentage of cells targeted (see Nagahara et al., page 1449, 1st col., 1st paragraph). Since Boden already demonstrate that LMP can induce bone formation and differentiation, an ordinary artisan would attach TAT to LMP so that LMP may cross cell membrane and reach target cells and alleviate the problem with gene therapy. The level of skill in the art is high as demonstrated by Nagahara, TAT fusion proteins may be transducted to a variety of cell types. An ordinary would have reasonable expectation of success to attach TAT to LMP and administering it in an effective amount to induce bone formation and differentiation in a mammal. One would be motivated to use osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP and LMP-1s, because Liu et al teaches that LMP-1(t) has identical effects as the full-length protein. WO99/06563 teaches that LMP induces bone formation in vivo. Furthermore, using hydrogel to load the fusion protein is routine practice to protect the protein from degradation. Moreover,

since Boden demonstrates that BMP-2 is increased up to 38 fold at protein level following LMP expression, and van Beuningen et al. have shown that proteoglycan level is increased following BMP-2 injection in an animal model, it would have been reasonable for an ordinary artisan to expect that following administration of TAT LMP to a mammal, the proteoglycan synthesis will be induced. Making the fusion protein and achieving predictable result would have been prima facie obvious to the ordinary artisan at the time the invention was made.

Response to Arguments Pertaining to 35 USC 103(a)

Applicant's arguments filed January 8, 2010 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

The LMP-1(t) taught by Liu is the same as LMP-1s in Hair, and the Examiner has recognized that Hair does not teach the claimed methods.

The Examiner agrees that Hair et al teach a truncated version of LMP-1, and therefore has withdrawn Liu et al from the rejection. However, the Examiner believes that Hair and Nagahara teach the limitations of the claims as described above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-9 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,858,431, in view of Nagahara et al.

Claims 7-9, 36-38 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,521,750, in view of Nagahara et al.

Claims 7-9 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 7,504,374.

Response to Arguments Pertaining to Double Patenting

Applicant's arguments filed January 8, 2010 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

The LMP-1(t) taught by Liu is the same as LMP-1s in Hair, and the Examiner has recognized that Hair does not teach the claimed methods.

The Examiner agrees that Hair et al teach a truncated version of LMP-1, and therefore has withdrawn Liu et al from the rejection. However, the Examiner believes that Hair and Nagahara teach the limitations of the claims as described above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-15, 21-30 and 36-40 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record. New claims 44-49 are added to the rejection.

Response to Arguments

Applicant's arguments filed January 8, 2010 have been fully considered but they are not persuasive.

The following grounds of traversal are presented:

The amino acid sequences for LMP-1, LMP-2, LMP-3, RLMP and LMP-1s have been disclosed in the prior art, and a person with ordinary skill in the art has sufficient guidance to identify amino acid sequences with osteoinductive potential. One of ordinary skill in the art would have understood from the instant disclosure that administering the claimed peptides to a cell would induce proteoglycan synthesis and osteoblast differentiation. Fig. 6. shows that peptides disclosed in the instant specification induce bone growth. A person having ordinary skill in the art would have reasonably inferred that the osteogenic effect of these peptides is likely due, at least in part, to these peptides' ability to induce BMP synthesis because BMP is known to play an important role in bone formation and growth. It is also well known that BMP increases proteoglycan production as well as induces osteoblast differentiation. Therefore, the person of ordinary skill in the art would have concluded that the peptides that induce bone formation (e.g., peptides with osteoiductive functionality) would also induce proteoglycan synthesis and osteoblast differentiation.

Furthermore, SEQ ID NOs: 1, 2 and 4-8 comprise the domain GAPPPADSA and would recognize its functional relationship to osteoinductive activity. Example 9 of the written description training demonstrates that a disclosed partial protein structure put the applicant in possession of the claimed genus.

Applicant's arguments have not been found persuasive for the following reasons.

One of with ordinary skill in the art would not have understood from the instant disclosure that administering of the claimed peptides to a cell would induce

proteoglycan synthesis and osteoblast differentiation or have osteoinductive potential, because the osteoinductive polypeptide can be less than 100% homologous to LMP-1, RLMP and LMP-1s. The specification does not provide adequate description of the structural and functional relationship of the region that comprises such activity.

SEQ ID NOs: 1, 2 and 4-8 comprise the domain GAPPPADSA, however, SEQ ID NO: 3 does not share that domain and also has osteoinductive potential. Also there is no teaching in the specification that this domain imparts osteoinductive potential upon these sequences. There is also no teaching in the art at the time of filing that this domain imparts osteoinductive potential. One of skill in the art would not necessarily know that this domain imparts osteoinductive potential. Applicants have aligned the sequences, but there are other conserved regions that applicants are ignoring, and with SEQ ID NO: 3 not having any conserved regions, it is unclear how one of skill in the art would know what sequences should be present in a polypeptide that is less than 100% homologous to LMP-1s. That is a broad genius that includes sequences that are only 1% homologous. It is also unclear how a sequence that is 1% homomologous could contain the GAPPPADSA domain.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele K. Joike whose telephone number is (571)272-5915. The examiner can normally be reached on M-F, 10:00-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michele K. Joike/
Primary Examiner, Art Unit 1636

Michele K. Joike
Primary Examiner
Art Unit 1636